Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7081–7084

Synthesis and characterization of an inherently chiral calix[6]arene in the 1,4-alternate conformation

Michael T. Blanda,* Lauren Edwards, Ralph Salazar and Mikki Boswell

Department of Chemistry and Biochemistry, Texas State University, San Marcos, TX 78666, USA

Received 19 June 2006; revised 18 July 2006; accepted 19 July 2006
Available online 14 August 2006

Abstract—An inherently chiral calix[6]arene possessing a C_2-symmetric A–B–H substitution pattern was synthesized via a two step process starting from the parent hexa-*t*-butylcalix[6]arene. The racemic, inherently chiral compound exists as a single isomer with the 1,4-alternate conformation. The inherent chirality was confirmed by treatment of the racemic compound with Pirkle's reagent to form diastereomeric complexes in solution.

1. Introduction

Calixarenes continue to be one of the most frequently used macrocyclic systems for constructing host molecules with tailored recognition properties.[1] However, *chiral* recognition by calixarenes represents a relatively unexplored area. Two general strategies have been employed to impart chirality to calixarene structures: appending chiral auxiliaries onto the achiral molecular framework or appending achiral moieties in an asymmetric substitution pattern onto the aromatic residues thereby creating inherently chiral calixarenes.[2] Pure optical isomers of inherently chiral calix[4]-[3] and calix[5]arene,[4] have been reported. In contrast, the earliest reports of inherently chiral calix[6]arenes did not attempt chiral recognition studies or resolution of the racemates.[5–7] However, Shinkai and co-worker were successful at resolving an inherently chiral calix[6]arene and demonstrated that Pirkle's reagent was effective in creating diastereomeric complexes with the racemic host.[8] Compared with the recent advances in chiral recognition by calix[6]arenes with chiral appendages,[9] chiral discrimination using inherently chiral calix[6]-arenes is undeveloped and warrants more attention.

Besides the inherent chirality of the calixarene framework, conformational isomerism is important when considering calixarene-based receptors. Of the various immobilized calix[6]arenes reported most are cone or 1,2,3-alternate conformers, but many intriguing host architectures can be envisioned based on the other shapes, especially the 1,4-alternate. Recently, Chen and co-workers have reported the crystal structure of an achiral 1,4-2,5-biscrown-4 calix[6]arene in the 1,4-alternate conformation.[10] Herein, we wish to report the synthesis, structural determination and NMR resolution of an inherently chiral calix[6]arene in the rare 1,4-alternate conformation.

2. Synthesis

Our strategy was based on the Gutsche method which provides a C_2-symmetric A–B–H substitution pattern of the aromatic rings.[5] Instead of the all-carbon chains with ester linkages, we chose to employ the more ionophoric ethyleneoxy ether tethers. In addition, we used *p*-cyanobenzyloxy groups rather than tolyl groups for further elaboration of the cyano groups (see Fig. 1). The first step involved 1,4- regioselective ether formation using potassium trimethylsilanolate as the base and α-bromotolunitrile as the alkylating agent to produce the 1,4-diether **2** in 90–95% yield.[11] When **2** was deprotonated with NaH and reacted with triethyleneglycol di-*p*-tosylate in acetone, the mono-bridged calix[6]-arene **3** was formed in approximately 30% isolated yield.[12] The racemic mixture was effectively separated using a CHIRALPAK AD-H chiral HPLC column with hexanes/2-propanol (9:1) as the eluent and the separation factor was calculated to be 1.1.

Keywords: Inherently chiral; 1,4-Alternate conformation; Calix[6]-arene; NMR resolution.
* Corresponding author. Tel.: +1 512 245 3121; fax: +1 512 245 2374; e-mail: mb29@txstate.edu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.07.087

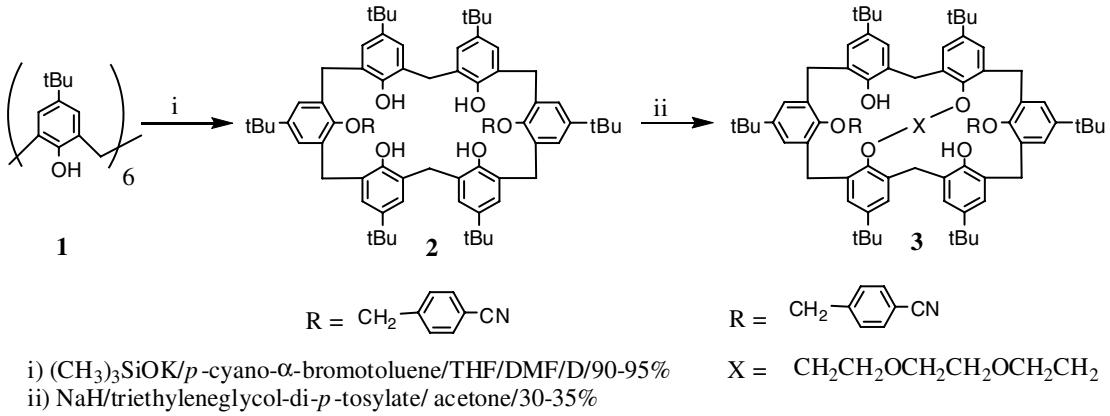

Figure 1. Synthetic route to inherently chiral compound **3**.

3. Solid state structure of 3

The solid state structure of **3** was determined by X-ray diffraction and is shown in Figure 2.[13] For purposes of this discussion, we define the A and D rings as the bridged pair, the B and E rings as the *p*-cyanobenzyloxy-substituted rings and the C and F rings as the unsubstituted phenolic rings. Visual inspection of the structure readily suggested that **3** adopted the 1,4-alternate conformation with the four *t*-butyl groups on the A, C, D, and F rings oriented downwards and the two *t*-butyl groups on the Band E rings pointed upwards relative to a line that passes through the oxygen atoms of the C/F rings. In addition to the conformation, the inherent chirality of the structure due to the C_2-symmetric A–B–H substitution pattern of the aromatic rings was also confirmed. A more rigorous classification of calixarene conformations was made by measuring the values and signs of the dihedral angles phi and chi between pairs of adjacent aromatic rings.[14] The values and signs for the six dihedral angles of **3** are listed in Table 1 and unambiguously describe the 1,4-alternate conformation wherein there are four pairs of *anti*-oriented rings and two pairs *syn*-oriented rings.

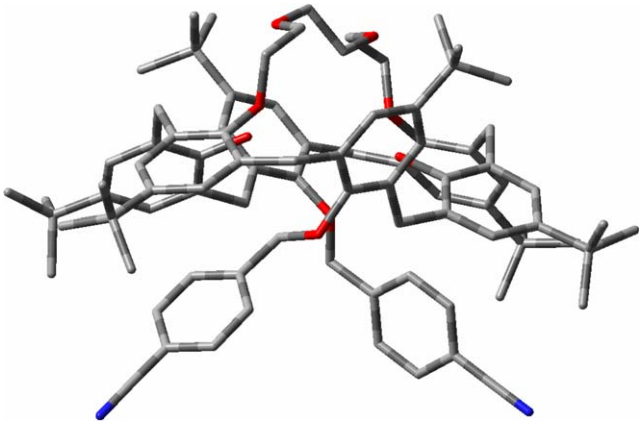

Figure 2. X-ray crystal structure of compound **3**. Hydrogens have been omitted for clarity.

Table 1. Conformational parameters φ and χ in compound **3**

Ring	Φ (degrees)	χ (degrees)	Orientation
A/B	146.9	133.8	*anti*
B/C	2.0	85.9	*anti*
C/D	98.7	−80.6	*syn*
D/E	150.8	122.2	*anti*
E/F	2.1	93.8	*anti*
F/A	99.3	−76.3	*syn*

4. Conformation of 3 in solution

In the ^{1}H spectrum ($CDCl_3$) at room temperature, the C_2-axis was evident by noting the three singlet resonances for the *t*-butyl groups and six doublets for the aromatic hydrogens of the calix framework. The C_2-symmetry was also consistent with the three resonances observed in the ^{13}C spectrum for the carbons of the ethylenoxy bridging unit and one resonance each for the benzylic and nitrile carbons of the *p*-cyanobenzyloxy groups.

Besides the molecular symmetry, ^{1}H and ^{13}C signals for the $ArCH_2Ar$ methylene bridges provided insight into the conformation of **3** in solution. Three signals were observed at 29.52, 31.75, and 38.72 ppm in the ^{13}C spectrum while an AX, AM, and AB quartet were observed for the diastereotopic methylene bridge hydrogens in the ^{1}H spectrum. The $\Delta\delta$s between the doublets were found to be 1.32, 0.63, and 0.12, which are commensurate with one *syn*-orientation, one intermediate *syn*/*anti*-orientation and one *anti*-orientation between the three contiguous rings.[11]

5. NMR resolution of 3

Titration experiments wherein successive amounts of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle's reagent) were added to racemic **3** in $CDCl_3$ clearly demonstrated the formation of two diastereomeric complexes at room temperature. The ^{1}H NMR regions for the aromatic (Ar–H, δ 6.3–4.7) and benzylic ($ArCH_2$-Ar and CH_2ArCN, δ 4.7–3.2) are shown in Figure 3 with

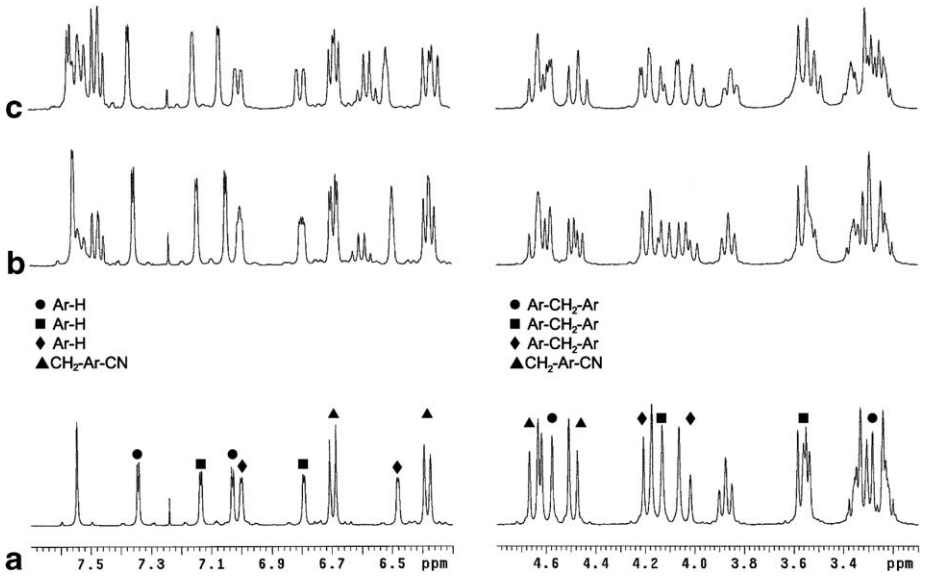

Figure 3. (a) Compound **3** with no Pirkle's reagent added. (b) Compound **3** with 1 equiv of Pirkle's reagent added. (c) Compound **3** with 2 equiv of Pirkle's reagent added.

coupled signals designated by matching symbols. Upon addition of 1 equiv of the Pirkle's reagent, the signals for the CH_2–*Ar*–CN protons were doubled and shifted slightly while aromatic resonances associated with the calixarene framework were only broadened. The $ArCH_2Ar$ signals were all affected significantly as well. At 2 equiv of Pirkle's reagent, additional changes to the spectrum were observed. Of the three pairs of doublets for the Ar–H protons of the calixarene rings, two (square and diamond) showed doubling of only one signal within a coupled pair and the third (circles) showed no doubling at all and not much broadening. Based on the doubling behavior of certain signals, it is tempting to conclude that Pirkle's reagent interacts preferentially with one side of the molecule.

Acknowledgements

We would like to thank the Robert A. Welch Foundation for financial support and Professor Carl Carrano at San Diego State University for providing the X-ray structure. The NSF-MRI program Grant CHE-0320848 is acknowledged for support of the X-ray diffraction facilities at SDSU.

References and notes

1. *Calixarenes 2001*; Asfari, Z., Bohmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic: Dordrecht, 2001.
2. Bohmer, V.; Kraft, D.; Tabatabai, M. *J. Incl. Phenom.* **1994**, *19*, 17–39.
3. Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Chem. Eur. J.* **2005**, *11*, 5917–5928.
4. Li, S.-Y.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron: Asymmetry* **2005**, *16*, 641–645.
5. Kanamathareddy, S.; Gutsche, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 6572–6579.
6. Neri, P.; Rocco, C.; Consoli, G. M. L.; Piattelli, M. *J. Org. Chem.* **1993**, *58*, 6535–6537.
7. Janssen, R. G.; Verboom, W.; Harkema, S.; van Hummel, G. J.; Reinhoudt, D. N.; Pochini, A.; Ungaro, R.; Prados, P.; de Mendoza, J. *J. Chem. Soc. Chem. Comm.* **1993**, *6*, 506–508.
8. Otsuka, H.; Shinkai, S. *J. Am. Chem. Soc.* **1996**, *118*, 4271–4275.
9. Erdemir, S.; Tabakci, M.; Yilmaz, M. *Tetrahedron: Asymmetry* **2006**, *17*, 1258–1263.
10. Guan, B.; Gong, S.; Wu, X.; Chen, Y. *Tetrahedron Lett.* **2005**, *46*, 6041–6044.
11. Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1992**, *57*, 3160–3166.
12. Into a round bottom flask was placed 3.34 g (2.78 mmol) of **2** along with 500 mL of acetone. To this was added 0.95 g (40 mmol) of sodium hydride (*Caution!*: flammable). Tri(ethyleneglycol)di-*p*-tosylate (1.82 g, 3.97 mmol) was dissolved in 100 mL of acetone and added over 45 min. The reaction was heated to reflux for 48 h and then the solvent was removed. The residue was re-dissolved in $CHCl_3$ and the solution was washed with 2 N HCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated to a minimal volume then poured into CH_3OH to precipitate the product. Isolated yields of 26–33% of **3** as a pure white powder were routinely obtained. The product was recrystallized from *n*-octane to obtain crystals suitable for X-ray diffraction. ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.54$ (s, 2H), 7.34, 7.03 (AXq, $J = 2.4$ Hz), 7.14, 6.80 (AXq, $J = 2.0$ Hz, 4H), 7.00, 6.48 (AXq, $J = 2.0$ Hz, 4H), 6.70, 6.38 (AXq, $J = 8.0$ Hz, 8H), 4.65, 4.49 (ABq, $J = 13.6$ Hz, 4H), 4.59, 3.26 (AXq, $J = 17.2$ Hz, 4H), 4.19, 3.56 (AMq, $J = 17.6$ Hz, 4H), 4.16, 4.03 (ABq, $J = 16.8$ Hz, 4H), 3.87 (t, $J = 10$ Hz, 2H), 3.51 (t, $J = 10$ Hz, 2H), 3.33–3.35, (m, 3H), 3.23–3.21 (m, 3H), 2.10 (t, $J = 10$ Hz, 2H), 1.42 (s, 18H), 1.17 (s, 18H), 0.89 (s, 18H). ^{13}C $\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta = 152.92$, 151.38, 150.02, 147.48, 145.84, 143.27, 141.78, 135.53, 133.20, 131.17, 131.08, 129.85, 127.51, 126.44, 125.31, 125.26, 125.16, 124.84, 124.07, 118.89,

71.42, 69.81, 69.57, 68.70, 38.72, 34.22, 33.98, 33.79, 31.79, 31.75, 31.46, 30.91, 29.53. Mp 260 °C (dec) $C_{88}H_{104}N_2O_8$ calcd: C, 80.24, H, 7.90. Found: C, 79.91, H, 7.88.

13. Crystallographic data, excluding structure factors, for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication (CCDC 602359). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit at CCDC.cam.ac.uk).
14. Ugozzoli, F.; Andretti, G. D. *J. Incl. Phenom. Mol. Recognit. Chem.* **1992**, *13*, 337–348.